# Effects of α-tocopherol and β-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study[1–3]

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**ABSTRACT** The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study was a placebo-controlled, randomized intervention trial testing the hypothesis that β-carotene and α-tocopherol (vitamin E) supplements prevent lung and other cancers. The study is predicated on a substantial body of evidence supporting a role in cancer prevention for these micronutrients. Based on the 2 × 2 factorial study design, 29 133 eligible male cigarette smokers aged 50–69 y were randomly assigned to receive β-carotene (20 mg), α-tocopherol (50 mg), β-carotene and α-tocopherol, or placebo daily for 5–8 y. Capsule compliance was high (median = 99%). β-Carotene treatment did not result in a decrease in cancer at any of the major sites but rather in an increase at several sites, most notably lung, prostate, and stomach (number of cases 474 compared with 402, 138 compared with 112, and 70 compared with 56, respectively). The vitamin E group had fewer incident cancers of the prostate and colorectum compared with the group not receiving vitamin E (number of cases 99 compared with 151 and 68 compared with 81, respectively), but more cancers of the stomach (70 compared with 56). In contrast to these intervention-based findings for β-carotene and vitamin E supplements, we observed lower lung cancer rates in men with higher amounts of both serum and dietary β-carotene and vitamin E at baseline. *Am J Clin Nutr* 1996;62(suppl):1427S–30S.

**KEY WORDS** Cancer, intervention trials, β-carotene, vitamin E, α-tocopherol, vitamins, antioxidants

## INTRODUCTION

The role antioxidant vitamins play in the prevention of cancer has been researched throughout the world for well over a decade. Originating with the observations of lower risk of cancer in persons consuming more fruit and vegetables (1–3) and the known biological properties of micronutrients such as β-carotene (4, 5), this field now encompasses a large number of randomized intervention trials designed to test the protective effects of antioxidants and other nutrients in human carcinogenesis. One such recently completed study is the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study, a large, double-blind, placebo-controlled cancer prevention trial of β-carotene and α-tocopherol (vitamin E) (6, 7). Along with data from other trials, the findings from this study add an important new dimension of information regarding the role vitamin supplements may play in the primary prevention of cancer. We summarize the results of the ATBC trial with respect to cancer incidence.

## SUBJECTS AND METHODS

### Trial design and baseline

The ATBC Cancer Prevention Study was conducted between 1985 and 1993 in southwestern Finland as a joint project between the National Public Health Institute of Finland and the US National Cancer Institute. The primary objective of this intervention trial was to evaluate the effects of β-carotene and vitamin E on the incidence of lung and other cancers. Study methodology and baseline characteristics of the ATBC Cancer Prevention Study population have been reported in detail elsewhere (6). A feasibility study was successfully conducted in one study area before the full-scale trial (8).

Participants were recruited through a postal survey and invitation scheme from 14 geographically contiguous areas of southwestern Finland. By June 1988, 29 133 white male smokers of five or more cigarettes daily and aged 50–69 y old had been randomly assigned to one of four study groups on the basis of the 2 × 2 factorial design: β-carotene alone (20 mg/d, as 10% water-soluble beadlets), vitamin E alone (50 mg/d, as 2-*ambo*-α-tocopherol), both agents, or placebo. This dosage of vitamin E is five times the recommended dietary allowance of the US National Research Council (9), and although there is no recommended dietary allowance for β-carotene, the dosage used is about three times the recommended dietary allowance for vitamin A. All capsules were contributed by Hoffmann-LaRoche, Basel, Switzerland. During screening visits, men were excluded if they had cancer (other than nonmelanoma skin cancer or carcinoma in situ) or other severe illness that would prevent full participation, were taking anticoagulants, or

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used vitamin supplements daily [vitamin E (> 20 mg), vitamin A (> 20 000 IU), or β-carotene (> 6 mg)].

At entry into the study, medical, dietary, smoking, and occupational data were obtained, along with physical measurements, a chest radiograph, and serum and toenail samples. All participants received counseling from the study nurses on the harmful effects of cigarette smoking. Dietary intake of β-carotene and vitamin E was estimated from a diet history questionnaire (10), and serum concentrations of β-carotene, α-tocopherol, and retinol were determined by HPLC (11).

### Follow-up

Active intervention continued through April 30, 1993, or for 5–8 y (median 6.1 y), and resulted in a total of 169 751 cumulative person-years of observation. Participation included three visits annually to the local study center. During the visit the men were asked about their health and possible subjective side effects, capsule compliance, and smoking habits since the last visit. The subjects were then given a new 4-mo capsule supply. Compliance was based on residual capsule counts (individual compliance) and was checked by random serum assessments (group compliance). A chest radiograph was taken at the 7th visit, 14th visit, and at the end of the study.

### Endpoints

Crucial to the success of any trial is endpoint ascertainment. Incident cancers occurring on or before April 30, 1993, were identified through the Finnish Cancer Registry on a census basis. Participants also contacted their study center if cancer was diagnosed in them. Medical records were retrieved from local facilities by study personnel and reviewed centrally by two study physicians who were blinded to intervention assignment. Random samples of these primary reviews were evaluated by independent oncologists. Pathology and cytology specimens were examined by relevant organ-system review groups for 92% of the cancers. Site-specific cancers were included in the analysis according to the intention to treat principle (ie, trial dropouts who developed cancer were identified and included according to their intervention assignment). Participants who developed two or more of the five primary cancers were counted as separate cases for each relevant site category regardless of other cancers but were counted only once within each category (including other cancers). Deaths were identified through the Central Population Register, and the underlying cause of death was obtained from death certificates. An independent data and safety monitoring board reviewed unblinded data concerning study endpoints and possible adverse reactions biannually throughout the trial.

### Statistical analysis

Standard survival analysis methods were used in this study, including proportional hazards models and computation of log-rank statistics (7). Preliminary site-specific cancers are presented as counts by β-carotene and vitamin E intervention assignment separately.

## RESULTS

Characteristics of the participants at randomization are shown in **Table 1**. The all-male study population was made up of older, middle-aged, long-term smokers of one pack of cigarettes daily on average. Dietary and alcohol intake and body mass index were comparable with other Western study populations, and serum β-carotene and α-tocopherol concentrations also were within normal limits. Median values of these and other baseline factors did not differ across intervention groups.

**TABLE 1**
Baseline characteristics[1]

| Index | Measurement |
|---|---|
| Age (y) | 57.2 ± 5.1 |
| Cigarettes/d | 20.4 ± 8.8 |
| Years of smoking (y) | 35.9 ± 8.5 |
| Body mass index (kg/m$^2$) | 26.3 ± 3.8 |
| Serum β-carotene (μmol/L) | 0.39 ± 0.34 |
| Serum-α-tocopherol (μmol/L) | 26.2 ± 8.4 |
| Serum retinol (μmol/L) | 2.05 ± 0.46 |
| Serum cholesterol (mmol/L) | 6.2 ± 1.2 |
| Daily dietary intake | |
| Total energy (kJ) | 11 778 ± 3293 |
| Total fat (g) | 122.9 ± 40.9 |
| Total fat (% of energy) | 39.0 ± 5.4 |
| β-Carotene (mg) | 2086 ± 1543 |
| Vitamin E (mg) | 11.5 ± 5.5 |
| Vitamin C (mg) | 105.9 ± 50.4 |
| Retinol (μg) | 1828 ± 1496 |
| Alcohol (g) | 18.0 ± 21.6 |

[1] $\bar{x}$ ± SD.

Capsule compliance was 99% in all groups during intervention. In the respective active treatment arms, serum concentrations for α-tocopherol increased at 3 y by 50% to 40.2 μmol/L, and β-carotene increased 17-fold to 5.59 μmol/L. Annual random blood sampling revealed that these concentrations remained constant throughout the trial. No change was noted in serum concentrations in the corresponding nontreatment arms.

By the end of the trial, 21% of the study population had quit smoking (defined as at least two consecutive visits when the study subject reported having stopped smoking), and this rate was equivalent across treatments. The overall study dropout rate was 30%, including deaths (12%), and varied little across intervention groups; 25 065 men (98.1% of those still alive) had an exit chest radiography.

Of the 3570 participants who died, 1851 were in the β-carotene arm and 1719 in the arm not receiving β-carotene; 1800 were in the α-tocopherol arm and 1770 in the arm not receiving α-tocopherol. The 8% excess in overall mortality in the β-carotene arm was statistically significant (95% CI: 1%, 16%; log-rank test, $P = 0.02$) and was attributed not only to lung cancer but also to ischemic heart disease and stroke.

Excluding nonmelanoma skin cancers and cases of multiple cancers, there were 2291 malignancies diagnosed. The numbers of incident cancers according to β-carotene treatment are shown in **Table 2**. We observed a statistically significant 18% excess in cumulative lung cancer incidence in the β-carotene arm by the end of the trial (95% CI: 3%, 36%; log-rank test, $P = 0.01$). Although the nature of this finding is still under investigation, and a general consistency appears to exist in the β-carotene effect across various subgroups (eg, age at randomization, study center, and diet), early analyses suggest that the lung cancer excess in the β-carotene group was evident primarily in men consuming more alcohol. β-Carotene showed no

**TABLE 2**
Incident cancers according to β-carotene intervention group

| Cancer site | Intervention assignment | |
|---|---|---|
| | β-Carotene | No β-carotene |
| Lung | 474 | 402 |
| Prostate | 138 | 112 |
| Bladder | 79 | 76 |
| Colorectum | 76 | 73 |
| Stomach | 70 | 56 |
| All others | 356 | 379 |

beneficial effect for other major cancer sites, and there were, in fact, increases suggested among β-carotene recipients for cancer of the prostate (23%) and stomach (25%).

Incident cancers according to vitamin E treatment are shown in **Table 3**. No overall effect was noted on lung cancer, with only 10 fewer cases in the vitamin E group by the end of the trial. We did, however, observe a statistically significant 34% reduction in prostate cancer incidence in the vitamin E group by the end of the trial (log-rank test, $P < 0.01$). Although no other statistically significant effects were noted from the vitamin E treatment, a reduction in colorectal cancer incidence (16%) and increase in stomach cancer (25%) were observed.

In contrast to these intervention results and consistent with prior epidemiologic studies, dietary intake and serum concentrations of β-carotene and α-tocopherol at study entry were inversely associated with subsequent lung cancer incidence rates in the control arm of the study. Restricting our analysis to the full placebo study group (ie, non–β-carotene and non–α-tocopherol), we observed lung cancer incidence of 47.9 compared with 39.9 per 10 000 person-years, respectively, for the lowest compared with the highest quartile of baseline dietary β-carotene intake, and 61.4 compared with 40.6 for low and high dietary vitamin E intake quartiles, respectively. A similar relation was observed and reported for serum β-carotene and α-tocopherol concentrations (7).

## DISCUSSION

To date, the results from other intervention trials of β-carotene are inconsistent. Some studies such as the recent, large trial in Linxian, China (12) showed prevention of stomach and overall cancer mortality with a daily supplement of β-carotene (15 mg), α-tocopherol (30 mg), and selenium (50 μg) for 5 y, whereas in the same population, a parallel study of high-risk persons in whom esophageal dysplasia had been diagnosed did not result in a similar protective effect (13). Several smaller trials suggest a beneficial effect of short-term supplemental β-carotene on oral premaligant lesions (14, 15), but larger, placebo-controlled trials have failed to show prevention of nonmelanoma skin cancer (16), colorectal adenoma (17), or sputum atypia (18) by supplemental β-carotene.

Results from the ATBC Cancer Prevention Study suggest that supplementation with β-carotene in middle-aged chronic smokers for an average of 6 y did not prevent the occurrence of lung cancer or other major cancers and in fact may have led to increased lung cancer incidence. These findings from a large trial are contrary to abundant epidemiologic data suggesting a beneficial relation between carotenoid intake and cancer (1–3), particularly lung cancer. There are several possible reasons for the finding and apparent discordance with previous epidemiologic research, most of which have been discussed (7, 19–23). Observational study data, which are supported by our own cohort findings concerning baseline serum and dietary β-carotene, may reflect the beneficial effects of certain long-term nutritional patterns on carcinogenesis occurring over a lifetime and may support the idea that longer supplementation is needed to achieve effective primary prevention. Findings such as those from the chemoprevention trial conducted in Linxian, China (12), however, suggest that even brief interventions of micronutrient supplementation in high-risk populations are capable of influencing disease; in this case, a reduction in total cancer mortality was observed within 5 y of the start of supplementation. Indeed, in our study, significantly lower prostate cancer incidence rates were observed in the vitamin E–supplemented group. Alternatively, other constituents of the fruit and vegetables identified as being beneficial, either alone or in some combination, may be the actual preventive components. The cumulative effect of lifelong cigarette smoking on lung carcinogenesis may, on the other hand, be too strong to be altered by short-term interventions late in life with micronutrients such as β-carotene. Other interpretations of our results for β-carotene include a lack of benefit for this substance, benefit only at doses lower or higher than that provided, and benefit or harm in selected population subgroups only, eg, those genetically susceptible or consuming more alcohol. For example, we are examining further the interaction between β-carotene and increased consumption of ethanol, based in part on prior evidence supporting adverse effects resulting from their combination (22). Preliminary results indicate that although alcohol use was identical across treatment groups, and therefore did not bias our results, higher alcohol intake may have led to increased lung cancer incidence in the β-carotene group.

In our study, vitamin E showed no overall effect on lung cancer; however, preliminary analyses indicate possible efficacy with longer duration of intervention. Prostate cancer incidence was 34% lower in the vitamin E group and colorectal cancer was 16% lower, the latter being consistent with recent observational data suggesting such a protective association (24, 25). Such effects, if corroborated by other studies, would have substantial public health consequences on two common malignancies. As previously reported, we also observed higher mortality from hemorrhagic stroke in participants receiving vitamin E, consistent with the known effect of vitamin E on platelet function.

This large trial of male smokers in Finland raises the possibility that supplementation with β-carotene and vitamin E has both beneficial and harmful effects in certain populations. Longer

**TABLE 3**
Incident cancers according to α-tocopherol intervention group

| Cancer site | Intervention assignment | |
|---|---|---|
| | α-Tocopherol | No α-tocopherol |
| Lung | 433 | 443 |
| Prostate | 99 | 151 |
| Bladder | 81 | 74 |
| Colorectum | 68 | 81 |
| Stomach | 70 | 56 |
| All others | 378 | 357 |

observation of ATBC Cancer Prevention Study participants is essential and has been initiated to assess postintervention trends in cancer incidence and in the occurrence of other endpoints, as well as to further understand the observed spectrum of effects of these agents. Furthermore, each cancer site will be evaluated in greater detail, for example, by looking at cancer stage and histology, and the possible modifying effects of various study factors such as intensity of smoking, dietary intake of vitamins, alcohol use, and duration of intervention. Data from several other ongoing, large prevention trials (26–28) will be essential for determining the role of β-carotene and vitamin E supplements in the primary prevention of cancer.

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